REMARKS

Status of the Claims

Claims 1-18 and 29-30 are currently under consideration.

Claim 1 and claims dependent thereon are amended herein to clarify that the antibody fragments intended to be encompassed by the claims herein are modified Fab' fragments. Claim 1 also is amended to more accurately recite the PEG derivatives that can be used as effector molecules in the present application. This amendment is consistent with the definition of "derivative" at page 8 lines 1-4 of the specification as originally filed

The withdrawal of the previous objection to the specification, as stated at page 2 of the Office Action, is noted with appreciation.

Claim rejections – 35 U.S.C. § 103

Reference is made to the Declaration of David P. Humphreys, submitted herewith. Journal articles referred to in that Declaration and not already of record in this case are provided with an Information Disclosure Statement submitted herewith.

The present invention arises from research directed to a more efficient way of providing an effector molecule such as PEG at the hinge region on a Fab' fragment. It was known that in order to attach a PEG molecule to the hinge, the cysteine at the hinge would have to be reduced to a thiol. At the time of the invention, it was common wisdom in the art that the interchain disulfide bond between the heavy and light chains had to remain intact during this reduction step in order to preserve the antigen-binding affinity of the Fab' fragment. It was believed that if the interchain bond were absent, then the light chain would disassociate from the heavy chain *in vivo*, particularly once the molecule was PEGylated. Therefore, reduction reactions on the Fab' fragment to reduce the hinge cysteine were carried out under mild conditions, so that only the hinge cysteine and not the interchain bond cysteines would be reduced. These mild reactions conditions resulted in inefficient PEGylation. (Humphreys ¶3).

Prior to the time of the present invention, mutations to create Fab' antibody fragments lacking inter-chain (LC-HC) bonds were known, but these Fab' fragments were intended to form $F(ab')_2$ dimers and had not been PEGylated. Specifically, Rodrigues et al (1993) and WO 99/15549 taught that Fab' lacking inter-chain disulfide bonds could be expressed and purified using normal methods. Both of these references are directed to improving the efficiency of $F(ab')_2$ formation *in vitro* from Fab' fragments. Neither Rodriguez et al. (1993) nor WO 99/15549 taught or suggested PEGylation of those Fab' fragments, although WO 99/15549 taught PEGylation of certain species of di-Fab'. Neither of these works taught or suggested that Fab' lacking inter-chain disulfide bonds might be suitable for *in vivo* applications. (Humphreys ¶4) Other references from that time period demonstrate the then-prevailing belief in the importance of maintaining the interchain disulfide bond. In particular, it was known that certain light chain dimers were associated with particular diseases, which indicated that light chain loss or exchange from a Fab'-PEG molecule with no interchain disulfide bond was a risk.Indeed, the art at the time suggested that the natural inter-chain (LC-HC) disulphide might indeed be required for full stability of molecules with longer circulation times, thus teaching one skilled in the art away from the use of fragments having no inter-chain covalent bonds. (Humphreys ¶5) This suggested that the absence of an inter-chain covalent bond presented at least some risk of LC loss or exchange in circulating serum. The inventors were uncertain as to how robust Fab-PEG lacking inter-chain (LC-HC) bonds would be during circulation in serum over 1-2 weeks. (Humphreys ¶¶5, 6)

At the time of the present invention, little was known about how to predict the serum circulation half-life of antibody and Fab molecules with altered structures. It was known that 'unstable' molecules such as scFv and human IgG4 were prone to 'domain exchange' both *in vitro* and *in vivo*. Since the long serum permanence was conveyed by the PEG molecule which was covalently attached to the heavy chain, it seemed highly plausible that in Fab'-PEG lacking inter-chain (LC-HC) bonds the light chain might be exchanged or lost in the circulation. This would have resulted in loss of antigen binding function (loss of efficacy) or increased clearance of the protein through precipitation, aggregation or proteolysis. (Humphreys ¶8)

The inventors herein modified both the light chain and the heavy chain of the Fab' fragments by replacing the cysteines that had formed the inter-chain disulfide bonds with other amino acids, thereby destroying the interchain bond. As the interchain cysteines were no longer present, it was possible to use stronger reaction conditions during the reduction of the hinge cysteine to the thiol, allowing for more efficient PEGylation at that site. Surprisingly, the modified Fab'-PEG molecules having no covalent bond between the light and heavy chains were active and stable in the circulation of mice for up to 7 days. Further, there was no loss of antigen binding affinity. This result was wholly unexpected, because the literature at the time suggested that the absence of an interchain bond would result in instability of the fragment in terms of loss or exchange of the light chain in vivo. It was believed that this instability could be even greater if a large PEG effector molecule was bound to the hinge. (Humphreys ¶10)

The present claims are directed toward modified Fab' fragments, characterized in that the heavy chain in the fragment is not covalently bonded to the light chain, and further in that *both* the interchain cysteine of C_L *and* the interchain cysteine of C_H1 have been replaced with another amino acid, the hinge region contains one or two cysteines, and wherein at least one PEG or PEG derivative molecule is attached to the fragment. It has been found that despite the absence of any covalent linkage between the heavy and light chain and the attachment of one or more effector molecules, the fragments of the invention as recited in the present claims surprisingly perform comparably with wild type fragments in a number of *in vitro* and *in vivo* tests, including stability and affinity for antigen. (specification, at paragraph spanning pages 2-3).

The claims stand rejected as obvious under two combinations of references; these two grounds of rejection will be addressed in turn.

Chapman et al. in view of Humphreys et al.

The rejection of the claims as obvious over Chapman et al. (Nature Biotechnology, 17:780-783, 1999) in view of Humphreys et al. (J. Immun. Methods, 209:193-202, 1997) is respectfully traversed.

Chapman et al. discloses that Fab' fragments having *intact* inter-chain di-sulfide bonds and having a single PEG attached at the hinge region have improved half-lives without loss of antigen-binding affinity. This is consistent with the general understanding in the art at that time that the inter-chain bond had to be intact in order to maintain good binding affinity to antigen. (Humphreys ¶6) Chapman does not teach or suggest that any modification should be made to either the light chain or the heavy chain of the Fab' fragment. (Humphreys ¶10) Fig. 2 of the Chapman et al. disclosure specifically shows an intact covalent bond between the light and heavy chains, thus teaching away from the presently claimed invention. To one skilled in the art, this reference suggests that in order to have improved stability in vivo, an interchain bond is necessary. (Humphreys ¶10)

Humphreys et al. is directed to the formation of dimeric Fab's (i.e., $F(ab')_2$) in E. coli., because in clinical applications it is often desirable to have the increased effective binding affinity afforded by a dimeric Fab' (Humphreys et al. at p. 193, second column, lines 5-7; Humphreys ¶11). The reference also teaches that Fab' lacking inter-chain disulphide bonds could be expressed and purified using normal methods. (Humphreys ¶11) The disclosure examines the effects of various parameters, including hinge size and isotype, presence of interchain disulphide bond, Fab' expression levels, tail piece sequences, and growth conditions. Noticeably absent from the parameters investigated by Humphreys et al. is the presence or absence of effector molecules of any kind. Further, Humphreys et al. found that the *unmodified* $\gamma 1$ hinge gave the greatest $F(ab')_2$ yield *in vivo* (p. 198, second column, lines 41-43). Thus, Humphreys et al. teaches *away* from modification of the hinge region.

Applicants respectfully submit that the rejection is based on impermissible hindsight, using the applicants' invention as a template to piece together unrelated elements from other disclosures, in a manner not taught or suggested by the prior art. Chapman et al. teaches PEGylated Fab' fragments with *intact* heavy chain – light chain bonds. Humphreys et al. teaches modification of Fab' fragments having *no effector molecules attached* in order to prepare $F(ab')_2$ fragments. These two endeavors have different goals. There is no reason why one interested in PEGylated antibody fragments of any type would have turned to the Humphreys et al disclosure. (Humphreys ¶12) Nor

would Humphreys et al.'s disclosure of modified hinge regions and the lack of a light-chain-heavy chain bond have suggested anything to the skilled artisan about the effects thereof on PEGylation. Nor would one skilled in the art have preferentially selected these aspects of the Humphreys et al. disclosure rather than any of the other parameters studied in the disclosure, i.e., effect of hinge size, Fab' expression levels, tailpiece sequences, and growth conditions. (Humphreys ¶12) There is simply no reason why one studying the Chapman et al. disclosure relating to PEGylated fragments, would have turned to the Humphreys et al. article, and would have randomly focused on two out of six parameters reviewed therein, to arrive at the presently claimed invention. (Humphreys ¶12) Nor would there have been any expectation that Fab' fragments having *both* of the heavy and light chain cysteines replaced with another amino acid would have had the same antigen affinity as wild type fragments. (Id.)

The Action states that one skilled in the art would have combined these references because Humphreys teaches that replacement of the interchain cysteines with serines minimizes incorrect interchain disulphide bonds between hinge regions and other cysteines. Yet the possibility of incorrect disulphide bonds arises in the context of dimerizing the Fab' fragments to form di(Fab')$_2$. It is not a consideration when the fragments are to remain in the format Fab'. (Humphreys ¶13) This aspect of Humphreys does not provide a reason why one skilled in the art would combine these two references.

It is therefore requested that this ground of rejection be withdrawn.

Singh et al. in view of Hsei et al. and Humphreys et al.

The rejection of the claims as obvious over the combination of Singh et al. (Analytical Biochemistry, 304(2): 147-156, May 15, 2002), in view of Hsei et al. (WO 98/37200, 8/27/98) and Humphreys et al., cited above, is respectfully traversed.

The combination of the Singh, Hsei, and Humphreys references does not teach or suggest the present invention. The disclosures of each of these references will be discussed first singly, then in combination.

(a) The Singh reference

Singh et al. teaches a method of labeling whole antibodies, with non-selective selenol-catalyzed reduction employing labels such as biotin-PEO-maleimide complex having a formula weight of 525.6. The catalyzed reduction resulted in the addition of seven labels in less than 5 minutes. The labeled antibodies of the Singh disclosure are different from the conjugated antibody fragments of the present invention in three important respects.

First, in the antibodies of Singh the cysteine residues of the interchain bond have not been replaced with another amino acid. Instead, the cysteine residues of the interchain bond are reduced at the same time as the cysteines in the hinge region, in order to create a thiol group that will accept a label. (Humphreys ¶15a)

Second, conjugating effector molecules to a Fab' fragment presents different challenges than labeling a whole antibody. (Humphreys ¶15b) A Fab' fragment, having no constant region extending beyond the hinge region, would be expected to be more subject to destabilizing effects of conjugated molecules; one skilled in the art would have expected the heavy and light chains to be pulled apart if there were one or more molecules attached to them and there was no covalent bond between them. Thus, results obtained with conjugation of molecules on whole antibodies can not necessarily be used to predict the effect of conjugation of effector molecules to antibody fragments. (Id.) The teachings of Singh relating to conjugated whole antibodies would not teach or suggest to one of ordinary skill in the art of conjugated antibodies and antibody fragments that similar results could be achieved with conjugated fragments having no covalent bond between the heavy and light chains and no constant region beyond the hinge. It is also significant that Singh does not teach the utility of said modified molecules *in vivo*. (Id.)

Third, the labels used in Singh were very different from the effector molecules recited in the present claims. The label molecules of Singh were biotin-PEO-maleimide having a formula weight of 525.6Da (Singh, page 149, left column, lines 5-9). By contrast the effector molecules described in the present application are PEG or PEG derivatives having a molecular weight of at least about 5,000Da, effectively a ten-fold increase, and the effector molecules used in the examples as described in the present specification were much larger. One of ordinary skill in the art would appreciate that the results achieved by Singh using *small* molecules with *whole* antibodies could not be used

to predict the results that would be achieved using *large* effector molecules with Fab' antibody *fragments*. (Humphreys ¶15c)

Contrary to the Examiner, the teachings of the secondary references Hsei and Humphreys do not make up for the deficiencies of Singh, as explained below.

(b) <u>The Hsei reference</u>

Hsei is cited (Action, p. 9, lines 7-10) for teaching antibody fragments "conjugated to two or more PEG molecules, and wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and the PEG molecules are attached via a cysteine residue or residues engineered into a selected site or selected sites in the antibody fragment…." This sentence is a collection of several disparate teachings of Hsei relating to different embodiments disclosed, although not exemplified, therein. In fact, the only embodiment disclosed in Hsei in which an interchain cysteine is replaced with serine is when the other interchain cysteine is bonded to an effector molecule. Hsei teaches that, at most, only one of the interchain cysteines is to be replaced with a serine, and that is to happen only when the other interchain cysteine is PEGylated (p. 23, lines 4-14; p. 24, line24 – p. 27, line 7). Thus, Hsei teaches away from the claim limitation that both interchain cysteines are to be replaced. And Hsei provides no working example of an embodiment wherein one of the interchain cysteines is replaced, and no working example of a Fab' fragment with more than one effector molecule. (Humphreys ¶¶16, 17) Hsei teaches nothing about modification of the interchain disulfide bond when the PEGylation takes place at the hinge, and provides no teaching or examples of antibodies or fragments in which the interchain cysteines on both the light chain and the heavy chain have been replaced. (Humphreys ¶15) Thus, this reference teaches away from the presently claimed invention in which both interchain cysteines are replaced.

Hsei teaches the following (emphasis added):

- *F(ab')*^{2} fragments having no more than about two polymer molecules, wherein every polymer molecule is attached to a cysteine residue in the light or heavy chain that would ordinarily form a disulfide bridge linking the light and heavy

chains (p. 23, lines 4-8; p. 24, line 24 – p. 25, line 32; p. 33, line 33 – p. 35, line 6). F(ab')^2 fragments are not within the scope of the present claims.

- Fab, Fab', and Fab'-SH fragments having no more than one polymer molecule, wherein the polymer molecule is *coupled to a cysteine residue in the light or heavy chain that would ordinarily form a disulfide bridge* linking the light and heavy chains (p. 23, lines 9-14; p. 25, line 33 – p. 27, line 7; p. 35, line 7 – p. 36, line 21). This means that the remaining cysteine residue that accepts the polymer molecule has not been replaced, and hence *both* cysteines which form the LC-HC disulfide bond have not been replaced as required by the present claims.
- Fab, Fab', and Fab'-SH fragment conjugates containing more than one polymer molecule, wherein every polymer molecule in the conjugate is attached to the hinge region (p. 23, line 15 – p. 24, line 23; page 31, line 25 – p, 33, line 32). There is no teaching or suggestion that *both* the interchain cysteines have been replaced, as required by the present claims.
- Fab, Fab', and Fab'-SH fragment conjugates containing no more than one polymer molecule, wherein the polymer molecule in the conjugate is attached to the hinge region (p. 27, line 8 – p. 28, line 4), with no teaching or suggestion that *both* the interchain cysteines have been replaced;
- Fab, Fab', and Fab'-SH fragment conjugates containing no more than one polymer molecule (p. 36, line 22 – p. 37, line 31), with no teaching or suggestion that *both* the interchain cysteines have been replaced.

At page 28, line 32 – page 30, line 5, Hsei generally discusses conjugates of antibody fragments with more than one PEG molecule, but does not discuss the type of fragments or where on the fragments the PEG molecules are attached. At page 30, line 6 – page 31, line 24, Hsei discusses Fab, Fab', Fab'-SH and F(ab')$_2$ fragments with more than one PEG molecule, but does not discuss where the PEG molecules are attached.

The present claims recite, inter alia, that *both* the interchain cysteines are replaced by another amino acid. By comparison, Hsei et al. teaches that the disulfide bridge is to be avoided by substituting another amino acid, such as serine, for the corresponding

cysteine residue in the opposing chain, *only* for those embodiments where the polymer molecule is bonded to the corresponding cysteine residue *in the heavy or light chain* (page 23, line 9-14; page 24, line 24 – page 27, line 7), which necessarily means that the other cysteine has not been replaced. Thus, even when one of the cysteines in the heavy or light chain is replaced, the other must be retained, because it forms the site of attachment of the polymer molecule. In all the other embodiments in which the polymer molecule is bonded to the *hinge* region*, Hsei says nothing about avoiding the disulfide bridge* between the heavy and light chains (page 23, line 15 - page 24, line 23; page 27, line 8 – page 28, line 4). Pages 37-38 are silent about the site of attachment of the polymer molecule or the presence or absence of the disulphide bond. Page 42 discusses avoidance of the disulphide bond so that a polymer molecule can be attached to the corresponding cysteine in the opposite heavy or light chain, indicating that the cysteine at the site of attachment was not replaced. Pages 98-102 discuss various steps in the preparation of the antibody. Pages 104-105 discuss compositions and administration of the antibody fragments.

Thus, Hsei makes the statement about the disulphide bridge being avoided only in the context of describing those embodiments wherein a polymer molecule is attached to a cysteine that otherwise would have been part of the interchain disulphide bond; and Hsei never suggests that both the heavy and light interchain cysteines are to be replaced with another amino acid, nor does Hsei suggest any reason for doing so.

(c) The Humphreys reference

The Humphreys et al. reference is discussed above. As noted, the Humphreys et al. reference teaches nothing about effector molecules in general or PEGylation in particular. Moreover, Humphreys et al. is specifically directed to using Fab' fragments to make $F(ab')_2$ fragments, which are excluded from the scope of the present claims as amended.

(d) The combination of references does not render the presently claimed invention obvious

The Action states at page 9 that “It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced anti-IL-8 Fab, Fab’, Fab-SH and $F(ab')_2$ fragments in which both the interchain cysteines of the CL and CH1 have been mutated to serines and the produced anti-IL-8 Fab, Fab’, Fab-SH and $F(ab')_2$ fragments comprise a modified hinge region containing one or two cysteines (e.g., SEQ ID No.: 1, 2 or 3) as well as a cysteine residue or residues engineered into a selected site or sites in the antibody fragment (i.e., in both the heavy and light chain constant regions) for PEGylation according to the selenol catalyzed reduction of disulfides as taught by Singh et al. for therapeutic benefit of inflammatory disorders.”

This statement is respectfully traversed. First, the Singh reference teaches a process that is not site-selective for placement of one or more effector molecules on an antibody fragment. Instead, Singh teaches that each and every cysteine residue on a whole antibody molecule is to be retained in the molecule and reduced so that a label molecule can be attached. Nor would one combine Singh et al. with Hsei. Hsei teaches that the interchain disulfide bond is to remain intact except for those instances where one of the interchain cysteines is replaced and an effector molecule is attached to the other interchain cysteine, although no working example of such an embodiment is presented.. There would be no reason to combine Hsei, which teaches PEGylation of fragments, with Singh, which teaches non-specific reduction and labeling of whole antibodies.

As noted above, the Humphreys et al. reference teaches nothing about effector molecules of any type, and is directed to ways of using Fab’ fragments to make $F(ab')_2$. Thus one seeking to provide PEGylated Fab’ fragments would have no reason to look to the teachings of Humphreys et al.

One of ordinary skill in the art would not be motivated to combine Singh with either Hsei or Humphreys, because one of ordinary skill in the art would not think that the teachings of Singh relating to total labeling of whole antibodies with small molecules would be applicable to the teachings of Hsei relating to selective PEGylation of antibody fragments with large effector molecules, or to the teachings of Humphreys et al. relating to methods of making $F(ab')_2$ fragments with no effector moelcules.

There is no reason why one of ordinary skill in the art would have been motivated to combine these references, especially when one considers that whole antibodies of Singh and $F(ab')_2$ of Humphreys fragments are *not part of the present invention*. Singh teaches small molecule labels on whole antibodies, not fragments, and complete labeling, not selective; Hsei teaches that only one interchain cysteine is replaced, not both, and only then when the effector molecules are to be attached at the opposite chain, not at the hinge; and Humphreys teaches non-PEGylated $F(ab')_2$ fragments. (Humphreys ¶18)

In response to the applicants' prior arguments, the Examiner noted that statements that PEGylation of interchain cysteines would destabilize the antibody fragment and force the heavy and light chains apart were mere arguments of counsel. Accordingly, the Declaration of David P. Humphreys is submitted herewith as evidence of these facts, and of the unexpected results achieved with the present invention, and why these results were unexpected. The Examiner also stated that the prior claim language encompassed not only Fab' fragments but any fragment that included an Fab' fragment, such as $F(ab')_2$ fragments. Accordingly claim 1 has been amended to clarify that only Fab' fragments are intended to be included within the scope of the claims. The comments of the Examiner at page 13 lines 22-29 regarding the Hsei reference relate only to the number of polymer molecules attached to the fragment, but fail to note that Hsei requires that at least one of the interchain cysteine residues remain intact. And in fact, essentially the only teaching in Hsei of removing an interchain cysteine in a Fab, Fab' or Fab'-SH fragment is at page 23, lines 9-14, out of a 185-page document, and no working examples are provided. Therefore the cited disclosure of Hsei taken in combination with the other references does not render the presently claimed invention obvious.

With regard to the comments at page 14 of the Action, Singh teaches a selenol reduction of all the cysteines in the antibody, including the cysteines at the interchain bond, and thus teaches away from the present invention, which teaches that these cysteines are to be replaced and specifically are not to be sites of effector molecule attachment. And even if one would have been motivated to combine the teachings of Hsei and Singh, that would not have led to the removal of both interchain cysteines, and Humphreys teaching of the making of Fab' dimers would have provided no motivation to

those looking to add effector molecules. There was simply no recognition in the art that the combination of these references would have resulted in some advantage, and in fact as explained in the accompanying declaration, the belief in the art at the time was that such a combination would lead to a significant disadvantage, namely, destabilizing of the molecule with attendant loss of half-life and loss of binding affinity. (Humphreys ¶18)

In view of the foregoing, where there is no reason to combine the cited references, and where such a combination would not yield the claimed invention, it is respectfully requested that the rejection under 35 U.S.C. 103 be withdrawn.

Double patenting

The double patenting rejection based on claims 7 and 10 of U.S 6,642,356 in view of Chapman et al. (1999) and Humphreys et al.(1997) is respectfully traversed. The only teaching of the '356 patent with respect to the interchain cysteines is that they are removed so that no incorrect bonds will be formed when the Fab' fragments dimerize to di-Fab'. The focus of the '356 patent disclosure is a peptide sequence that can be used as hinge regions in proteins, where they can be covalently coupled to achieve dimeric structures, for example, as found in antibodies. Independent claim 5 of the '356 patent recites an antibody fragment comprising one polypeptide chain having the recited amino acid sequence; claim 7 which depends on claim 5 recites that the fragment is a Fab or Fab' fragment, and claim 10 which depends on claim 7 recites the fragment with one or more effector or reporter molecules attached to it.

First, it is respectfully pointed out that the amino acid sequence recited in the claims of the '356 patent is not the same as the amino acid sequences of the present application. Moreover, SEQ ID NO:1 of the '356 patent contains *four* cysteines, yet claim 1 recites that the hinge region contains *one or two* cysteines. (Humphreys ¶19) Thus the claims of the '356 patent actually teach away from the presently claimed fragments.

Second, like the Humphreys 1997 article, the Humphreys '356 patent is directed to the production of di-Fab' structures from Fab' fragments, in which the interchain cysteines had been removed to prevent the formation of incorrect bonds during the dimerization process (Humphreys ¶17). Although PEGylation of the di-Fab' fragments

was attempted, the efficiency was so low as to be considered unworkable (Humphreys ¶18).

In response to the applicants' arguments, the Action states (p. 17 – p. 18) "The rejected claims do not recite or require any particular sequence and do not exclude the sequence of the '356 patent. Thus the sequence of the '356 patent reads upon the broader scope of the instant claims." This statement is respectfully traversed. While the instant claims do not recite or require any particular sequence, the instant claims do recite and require that the hinge region have only one or two cysteines. The sequences of the '356 patent have four cysteines, and thus could not be used in the Fab' fragments as presently claimed. (Humphreys ¶19)

As noted above, Chapman teaches that the interchain disulphide bond should remain intact, and Humphreys et al teach that there should be no interchain disulfide bonds so that there will be no incorrect bonds formed when the Fab' fragments dimerize; Humphreys et al. teaches nothing about PEGylation. Thus it would not have been obvious to modify the Fab or Fab' fragments of claims 7 and 10 of the '356 patent, those fragments having chain regions with four cysteine residues, and attach PEG molecules to the free cysteine thiols of SEQ ID NO:1, nor would doing so have resulted in the claimed fragments. One skilled in the art would not have thought that the advantages alleged to accrue in Chapman and Humphreys et al would accrue by making the suggested modificatins to '356 patent claims 7 and 10. The benefits of Chapman were achieved by leaving the interchain bonds intact. The benefits of Humphreys et al related to dimerization, not PEGylation.

The present invention is based on applicants' surprising discovery that a Fab' fragment could be produced having affinity for antigen comparable to wild type antibody and sufficient stability to survive in the circulation of an animal for 7 days, yet have no disulfide bridge between the heavy and light chains, and have the cysteines of both the heavy and the light chains replaced with another amino acid, and have one or two cysteines in the hinge region, and have an effector molecule attached.

As the U.S. Supreme Court has stated,

> "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application

> that claims as innovation the combination of two known devices according to their established functions, *it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does*. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) (emphasis added).

In this case, there is no reason to combine the '356 patent with Chapman et al. or Humphreys et al., nor would such a combination have resulted in the presently claimed fragments, because nothing in any of these references suggests that it would be desirable to have an Fab' fragment with no interchain bonds between the heavy and light chains, and with both cysteines in the heavy and light chains replaced with another amino acid, and with the hinge region containing one or two cysteines.

CONCLUSION

As all points of rejection have been overcome, a Notice of Allowance is respectfully requested. The Examiner is invited to contact the applicant's undersigned representative if it is believed that a conference might further the prosecution of this matter.

Respectfully submitted,

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